copy of the revised drawings are also attached to this Response.

Examiner's Paragraph 2:

The Examiner has noted that claim 1 contains periods within the claim. Applicants have amended claim 1 to remove the objectionable periods.

The Examiner has also noted that the acronym "PLS" is found in claim 1 and should be defined. Applicants have amended claim 1 so that the acronym is defined immediately after the words "partial least squares" appearing in step c.

Examiner's Paragraph 3:

The Examiner has rejected claims 1-3 under 35 U.S.C. 101 "...because the claimed invention is directed to non-statutory subject matter." In explaining this conclusion the Examiner states: "In instant claim 1, the claimed invention is drawn to collecting known pK_a for ionizable groups on a molecule followed by a mathematical method. The remainder of the instant claims is a standard prior art process of storing data in a database."

Applicants respectfully disagree with the Examiner's characterization of the invention and believe that a misunderstanding of the invention has led the Examiner to mistakenly conclude that the invention is directed to non-statutory subject matter. Applicants have not simply collected "known pK_a values for ionizable groups." as the Examiner states. On the contrary, Applicants have defined a molecular descriptor for molecules for which a pK_a is known consisting of a hierarchical connectivity tree which takes into account the number of times each atom type present is found in the tree at each hierarchical level. Such a descriptor is defined for each molecule in the training set. The molecular descriptor for each molecule is then placed in a data table where each descriptor is associated with the Pk_a of the molecule from which the descriptor is derived. The partial least squares statistical methodology is used to derive coefficients for each atom type at each hierarchical level found in the molecules of

the training set. The pK_a of a molecule not found in the training set is found by generating the hierarchical atom type connectivity tree noting the number of times each atom type occurs for that molecule and multiplying the number of occurrences of each atom type in the molecule of interest by the PLS coefficient determined for that atom type and summing the resulting multiplications to obtain the predicted Pk_a.

Applicants have amended claim 1 to more particularly point out and claim their methodology. With that amendment and the above description, Applicants believe they have clearly demonstrated that the invention is not non-statutory. Applicants submit that this new computer implemented methodology for determining the pK_a of molecules meets all the tests for determining statutory subject matter that have been promulgated by the courts. Accordingly, Applicants request that the Examiner withdraw the 35 U.S. C. 101 rejection.

Examiner's Paragraph 5:

The Examiner has reminded Applicants of their obligations under 37 CFR § 1.56. For the Examiner's information, all the inventors have assigned their rights in the invention to Tripos, Inc. for whom they worked at the time the invention was made. An assignment document reflecting Tripos' ownership will be filed at the time the issue fee is paid.

Examiner's Paragraph 6:

The Examiner has rejected claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over Martin et all. The Examiner states that: " Martin et al utilizes the Comparative Molecular Field Analysis (CoMFA) 3D QSAR method to determine the activity coefficients and subsequently the pK_a of various ionizable groups at each level. The interaction energies of the molecule of interest and its environment is also determined..... However, Martin et al. does not teach storing the data in a database."

Applicants respectfully submit that Martin et al. does not render Applicants' invention

obvious for two reasons. First, Applicants believe that the Examiner has misinterpreted Martin et al. Martin does not "...determine the activity coefficients" and does not determine "the pK_a of various ionizable groups at each level." Martin describes each molecule of the training set "...by its interaction energies with atomic probes at intersections of a lattice." (149 Abstract). These energies form rows in a data table and each row is associated with the pK_a of the molecule it represents. PLS analysis performed on this data table yields a coefficient for each lattice point which reflect the contribution of that lattice point to the pK_a. No activity coefficients are determined by Martin and there are no "levels" involved. Applicants' invention determines PLS coefficients associated with the atom types at each hierarchical level of an atom connectivity tree. The use of such a tree and atom type definitions to obtain a pK_a is not taught by Martin. Thus, except for the common use of PLS, Martin's method bears no resemblance to that of Applicants and can not render Applicants' invention obvious.

The second reason Martin does not render Applicants' invention obvious is that the underlying molecular descriptor used by Martin is entirely different than the molecular descriptor used by Applicants. Martin teaches the use of a molecular interaction energy field descriptor. Such a descriptor calculates the steric and/or electrostatic interaction energy between an atomic probe and the atoms of the molecule at each of the intersection points in a lattice placed around the molecule. Applicants' molecular descriptor, on the other hand, is a hierarchical atom type connectivity tree noting the number of times each atom type occurs for each ionizable group on the molecule. The atom fragment connectivity table which results from this hierarchical tree does not resemble in the slightest Martin's interaction energy table. Nowhere in the prior art, including the Martin et al. reference, is it taught that such an atom type hierarchical tree could be used to calculate a pK_a.

Finally, in performing a CoMFA analysis, Martin must necessarily use 3D structures. The 3D structures must have a similar conformation and be uniformly aligned in order to perform the analysis. No such use of 3D structures and no alignment is required to practice Applicants' invention. For all of the above reasons, Applicants submit that Martin et al. do not render Applicants' invention obvious. Accordingly, Applicants request that the Examiner withdraw the 35 U.S. C. 103(a) rejection.

Applicants submit that they have responded to and overcome all grounds for objection and rejection set forth by the Examiner. Applicants respectfully request that the Examiner allow the application and pass it to publication.

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Respectfully submitted,

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1. A software implemented methodology for determining the pK_a of a molecule of interest comprising the following steps:

a) determine the hierarchical atom type connectivity tree noting the number of times each atom type occurs for each ionizable group on each molecule of a series of molecules for which an experimentally determined pK_a is known;

b) place each of the determined atom types noting the number of times each atom type occurs for each hierarchically determined connectivity tree in a row of a data table along with the experimentally determined pK_a of the molecule from which the tree was determined;

c) using the partial least squares (PLS) statistical methodology, extract coefficients associated with each atom type represented at each hierarchical level;

d) determine the hierarchical atom type connectivity tree noting the number of times each atom type occurs for the molecule of interest; and

e) multiply the number of occurrences of each atom type in the molecule of interest by the PLS coefficient determined for that atom type and sum the resulting multiplications to obtain the predicted pK_a.

2. The method of claim 1 in which each atom type from the hierarchical atom connectivity tree in steps a and d for each ionizable group on each molecule is placed into a separate bin in a bit string.

3. The method of claim 2 in which the extracted coefficients are associated with the appropriate bin in the bit string.

Original claims with amendments shown by underlining and brackets.

1.(amended) A software implemented methodology for determining the pK_a of a molecule of interest comprising the following steps:

a)[.] determine the hierarchical atom type connectivity tree noting the number of times each atom type occurs for each ionizable group on each molecule of a series of molecules for which an experimentally determined pK_a is known;

b) place each of the determined atom types noting the number of times each atom type occurs for each hierarchically determined connectivity tree in a row of a data table along with the experimentally determined pK_a of the molecule from which the tree was determined;

c)[b.] using the partial least squares (PLS) statistical methodology, extract coefficients associated with each atom type represented at each hierarchical level;

d)[c.] determine the hierarchical atom type connectivity tree noting the number of times each atom type occurs for the molecule of interest; and

e)[d.] multiply the number of occurrences of each atom type in the molecule of interest by the PLS coefficient determined for that atom type and sum the resulting multiplications to obtain the predicted pK_a.

2. The method of claim 1 in which each atom type from the hierarchical atom connectivity tree in steps a and d[c] for each ionizable group on each molecule is placed into a separate bin in a bit string.

3. The method of claim 2 in which the extracted coefficients are associated with the appropriate bin in the bit string.